CLINICAL VIGNETTE

Nivolumab-induced Acute Interstitial Nephritis without Pyuria

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A 59-year-old man presented with acute kidney injury with a serum creatinine 3.1 mg/dL. His baseline creatinine, six weeks prior was 1.0-1.2 mg/dL and was 2.3 mg/dL two weeks prior. Past medical history includes BRAF negative metastatic melanoma to the right inguinal lymph nodes, external iliac lymph nodes, and lung. The patient completed four cycles of ipilimumab and nivolumab about four months prior. PET/CT showed interval significant decrease in size and metabolic activity of the right inguinal and external iliac lymphadenopathy and resolution of the left lower lobe hypermetabolic non-calcified nodule. He remains on maintenance nivolumab.

Treatment was complicated by grade 1 pruritic rash, low-grade cough, generalized fatigue, headaches, hypothyroidism and grade 2/3 diarrhea due to colitis. Budesonide was given. One month prior, budesonide was tapered and he started hydrocortisone 10mg daily for hypocortisolism. He was hospitalized four months prior for symptomatic anemia with melena, started on pantoprazole drip and octreotide. He had erosive esophagitis, chronic gastritis, and ulcers of the esophagus, stomach, and duodenum. He was discharged on pantoprazole 40mg PO BID for 6 weeks which was decreased to daily dosing.

Other past medical history includes peripheral neuropathy, peripheral artery disease s/p femoral-tibial bypass, hyperlipidemia, gout, and squamous cell carcinoma. Home medications included febuxostat 40mg daily, ferrous sulfate 325mg daily, gabapentin 600mg daily, hydrocortisone 10mg daily, icosapent ethyl 2 grams BID, levothyroxine 25mcg daily, pantoprazole 40mg daily, and rosuvastatin 20mg daily.

Vital signs and physical examination were unremarkable. Additional labs included WBC count 8.7 K/uL without eosinophilia, hemoglobin 14.9 g/dL, platelet count 287 K/uL, potassium 4.4 mmol/L, carbon dioxide 26 mmol/L, BUN 32 mg/dL and TSH 3.8 mclU/mL. Urinalysis showed RBC 0-5/HPF and WBC 0-5/HPF with urine protein/creatinine of 0.2. No urine eosinophils were seen. FeNa was 3.6% and FeUrea was 52%. Renal ultrasound was unremarkable with 13.6 cm right kidney and 13.7 cm left kidney without hydronephrosis.

Kidney biopsy revealed acute interstitial nephritis, acute tubular injury, low-grade mesangial IgA deposition of no clinical significance, and moderate arterio- and mild arteriolosclerosis.

Nivolumab was held indefinitely and prednisone 60mg daily was initiated and tapered over 3 months. Two weeks later, serum creatinine was 1.88 mg/dL, at one year the creatinine was 1.50 mg/dL, and at two years the serum creatinine improved to 1.27 mg/dL. At two years, his metastatic melanoma also remained in complete remission by circulating tumor DNA study parameters and PET/CT imaging. Brain MRI with and without contrast did not show metastatic disease. He remained on pantoprazole 40mg PO daily throughout the follow-up period.

Discussion

Immune checkpoint inhibitors (ICIs) block intrinsic down-regulating receptors of the immune system and activate suppressed T-cells to enhance antitumor-directed immune responses. Pembrolizumab and nivolumab are ICIs that block anti-programmed cell death receptor-1 (PD-1). Nivolumab is indicated in the treatment of many cancers including colorectal cancer, esophageal, gastric, head and neck, hepatocellular carcinoma, Hodgkin lymphoma, malignant pleural mesothelioma, melanoma, merkel cell carcinoma, non-small cell lung cancer, renal cell carcinoma, and urothelial carcinoma.[1]

While our patient presented with some of the more common ICIs toxicities including fatigue, rash, hypothyroidism, adrenal insufficiency, and colitis, he also developed acute kidney injury seven months after initiating treatment. The estimated incidence of ICI-associated AKI is 3.7%[2] and the onset of AKI seen with PD-1 inhibitors is usually late (3-10 months).[3] The large variation in time-to-disease from treatment initiation is thought to be due to a long half-life of 2-3 weeks.[4] In one multicenter study, acute interstitial nephritis was the dominant finding in 93% of 60 patients biopsied with approximately half presenting with pyuria.[5]

In addition to withholding use of ICIs, oral prednisone 0.5–1 mg/kg/day is typically started with a maximal dosage of 60–80 mg daily and tapered over 8-12 weeks. Severe cases are defined by initiation of renal replacement therapy, serum creatinine 3 times baseline, serum creatinine >4.0mg/dL, urine output <0.3 mL/kg/h for ≥24 h, or anuria for ≥12 h. In these patients, IV methylprednisolone 0.5–1.0 g/day for 3 days must be implemented.[4] Patients treated with corticosteroids had complete, partial, or no kidney recovery in 40%, 45%, and 15% of patients.[5]

Because ICIs may be the only available therapeutic option, 22% of patients with ICI-related AKI are rechallenged with the same

ICI or switched to a different one with or without low-dose corticosteroids.[6] Interestingly, 83.5% of patients in one study did not have recurrence of AKI when rechallenged and there was no difference in survival among patients rechallenged and not rechallenged following ICI-associated AKI.[7]

While acute interstitial nephritis is the most common etiology of ICI-associated AKI found on kidney biopsy, rare cases of acute tubular injury alone and glomerular disease have been reported. A systematic review and meta-analysis reported 45 cases of biopsy-proven ICI-associated glomerular disease with 27% pauci-immune glomerulonephritis, 24% podocytopathies, and 11% C3 glomerulonephritis.[8]

Conclusion

With increasing use of ICIs for treatment of malignancies, ICI-associated AKI is becoming more common. ICI-associated acute interstitial nephritis is managed by holding the offending agent and initiating corticosteroids to avoid significant morbidity and mortality. In patients in which ICIs are the only therapeutic option, rechallenging with the same or a different ICI can be considered with close monitoring and prompt treatment for recurrence of AKI.

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